Requirements of the

- European Medicines Evaluation Agency -

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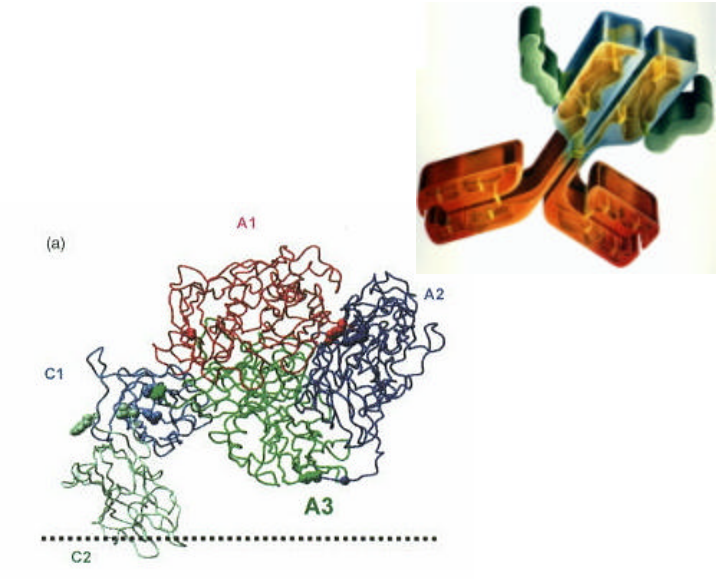

Questions

1) What are the EU requirements regarding potential inhibitor formation induced by factor VIII products, for
   a) preclinical testing,
   b) clinical trials, and
   c) post-marketing surveillance?
2) What was the rationale for selecting clinical trial parameters such as number of patients enrolled?
3) How does the EU assess the potential for inhibitor formation induced by factor VIII products?

Preclinical Testing ?

- Assessment by laboratory tests ?
  - Extensive characterization of novel products
  - Proposal for specific tests based on experience with a double-inactivated (SD + past.) FVIII causing a cluster of inhibitors:
    - slower FVIII cleavage by thrombin, more rapid Xa generation, enhanced PL binding (NIBSC data)
    - 40 kD impurity (company)
  - So far no established predictive test available

Animal Studies ?

- Assessment by animal experiments ?
  - Ordinary animal studies are not helpful due to species differences of immune response
  - Studies in non-human primates are no solution
    - Difficult design (number of animals, duration); very costly
    - Still uncertainty about meaning of results
  - Will new models with transgenic animals be helpful ?

Clinical Trials

- **CPMP Blood Product Working Group (BPWG)**
  - notes for guidance (NfG) on clinical assessment of products (“licensing studies”) ; examples:
    - **NOTE FOR GUIDANCE ON THE CLINICAL INVESTIGATION OF HUMAN PLASMA DERIVED FACTOR VIII AND IX PRODUCTS (*)**
    - **NOTE FOR GUIDANCE ON THE CLINICAL INVESTIGATION OF RECOMBINANT FACTOR VIII AND IX PRODUCTS (*)**
  - core SPCs
  - scientific advice to applicants

(*) *http://www.emea.eu.int*

No longer formal requirement for PUP Studies

- Donor selection, testing and manufacturing steps are now considered to be highly effective and demonstrative of the viral safety of the product with respect to enveloped viruses. Therefore it is no longer considered appropriate to use clinical trials to investigate viral safety with regard to enveloped viruses.
- The procedures may be of limited value against non-enveloped viruses, such as Hepatitis A and Parvovirus B19. However, the safety of the products with respect to non-enveloped viruses cannot currently be adequately evaluated in clinical studies.

Assessment of Product-Related Inhibitors in PTP

- In PUP, patient related factors (e.g. certain types of mutations, family history) appear to be more important determinants of inhibitor development than the product.
- Two inhibitor ‘outbreaks’ occurred in the early 1990’s in previously tolerant patients who were switched to plasma derived products subjected to modified virus inactivation. It was **apparent from this experience that the risk of inhibitor formation related to an individual product can be evaluated in (PTPs)**.
- Recommendation to study in PTPs and not PUPs

Assessment of Immunogenicity

- At least 50 PTP > 12 years of age, with factor VIII ≤2%, being immunocompetent (CD4 lymphocytes >400/µl), with at least 150 treatment exposure-days to previous products, to be followed for at least 50 exposure days or 6 months whichever is sooner.
- FVIII consumption and efficacy
- The factor VIII inhibitor titre should be determined at baseline and every 3 months.
- The titer of the inhibitor should be reported in Modified Bethesda Units (BU) [(1)]. Plasma samples of patients who are suspected of inhibitors or who have developed inhibitors should be stored.
- Studies to be performed according to GCP

1) Thromb-Haemost. 1998 Apr; 79(4): 872-5

Treatment of Children

- Since children may respond differently compared to adults, an open multicentre **phase IV trial should include at least 20 children under the age of six years** regardless of prior treatment. The children should be tested for inhibitors every 3 months or if there is any suspicion of inhibitor development. The FVIII consumption (dose/kg for prophylaxis and therapy (on demand)) should be monitored as well as development of inhibitors.
- The trial should **not be started until data are available** on 50 exposures for 20 patients (older than 12 years) who are included in the **PTP trial**. The study in children should continue until the patients have received at least 50 exposures to the product or have been treated for 6 months whichever is sooner.

Special Treatment Modalities

- If the posology **continuous infusion therapy** is requested, clinical data are required to establish the efficacy and safety.
  - At least 12 haemophilia A patients undergoing elective major surgical procedures. Pharmacokinetic study to determine the rate of infusion performed prior to surgery. Efficacy and safety data during surgery and for at least 6 days thereafter.
  - There have been preliminary reports about enhanced inhibitor formation (ISTH SSC)
- Any request for an indication of **induction of immune tolerance** in haemophilia A patients with inhibitors should be accompanied by clinical data.

Post-marketing Phase

- To ensure consistency between data from the clinical studies and from routine use, a **post-marketing study** to assess clinical efficacy, immunogenicity and safety should be undertaken and a protocol submitted with the dossier. The results of the PTP study should be taken into account in the design of this study.
- FVIII products are subject to regular post-marketing controls (Directive 2001/83/EC), e.g.:
  - Pharmacovigilance system, collecting any information on suspected adverse reactions, keeping records and reporting to authorities
  - Periodic Safety Update Reports (PSUR): six monthly within first two years, annually the following two years, at renewal (after five years)

Product Information

- Incidence of inhibitors in PUPs and maximum inhibitor titre (above or below 10 BU).
- Any inhibitor development in PTPs

PTP Inhibitors: Reports to the PEI

- In **1995** (*), there were **no reports**
- In the period **2000 to 2003**
  - cases with **p**lasma derived **p**roducts: 10
  - cases with **r**ecombinant **p**roducts: 62

(*) Prompted by an inhibitor cluster with a double-inactivated FVIII concentrate, the PEI asked MA-holders about cases of inhibitors in PTP

EU Review of Inhibitor Patients under Treatment with rhFVIII

- The CPMP noted a number of reports of inhibitors in PTPs and adult patients treated with rFVIII products and decided that this topic should be critically looked at.
- Therefore, the CPMP agreed upon a **request for information**, which should be forwarded to the MAHs of rFVIII products via the Rapporteur/Reference Member State in order to update the information on inhibitors in patients treated with rFVIII products.
- Responses will be considered by PhVWP, BPWG and CPMP in the next few months.

Review of Inhibitor Patients under Treatment with rhFVIII

- Questions to be addressed by companies
  - World-wide cumulative number of reports of inhibitor development in PUPs and PTPs
  - Cumulative information on inhibitor patients
  - Cumulative worldwide patient exposure to each rFVIII product and the number of units distributed worldwide
  - Narrative Information on individual cases of inhibitors in PTPs (presented in CIOMS Form)

Rationale for Selecting Clinical Trial Parameters

- The focus on PTP is based on experience with product-related inhibitor clusters
  - assessment of inhibitor titers with modified Bethesda assay (incubation for 2 h), to detect type 2 inhibitors
- The number of 50 PTP is a compromise between statistical considerations, and availability of patients in EU member states
  - inhibitor cluster in Germany 12 of 141 treated PTP
  - compulsory post-marketing study
- Phase IV study in children, since there is no more a formal requirement for PUP studies

Assessment of the Potential for Inhibitor Formation

- So far, EMEA did not implement nor identify any preclinical testing predicting neoantigenicity.
- The current guidelines for clinical assessment focus on detection of inhibitors in PTP; the requirements will be kept under continuous review.
- Review of existing information on occurrence of inhibitors is underway.